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Determinants of baPWV

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2) Characteristics of PWV and AI among various stage of hypertension 23 May, 2010. The Pulse of Asia in 2010, Tokyo, Japan

Abstract

Arterial stiffness is one of the biggest predictors of coronary heart disease (CHD). We evaluated whether brachial-ankle pulse wave velocity (baPWV) and augmentation index (AI) are correlated with risk factors of CHD. All of the 528 participants (270 males and 258 females) of this study were healthy workers aged from 36 to 69 (mean age: 47.9±8.1 years). The Framingham Risk Score (FRS) showed a good correlation with baPWV ($r=0.53$, $p<0.01$), indicating that FRS is applicable as an index of arterial stiffness also in Japanese. Blood pressures were well controlled in patients with medical treatment for hypertension; however, vessels remained relatively still stiff, while the AI was considerably low. Multivariate linear regression analysis showed that factors of such as FRS, body mass index, alcohol consumption, and AI P75 were significantly correlated with baPWV.　(134 words)

Introduction

Hypertension, hypercholesterolemia and smoking are the three biggest risk factors of coronary heart disease (CHD) according to the Framingham Study. Additionally, the Framingham Risk Score (FRS) was developed to predict the 10-year risk of CHD in a person aged 30-74 years without atherosclerotic CHD (1,2). It is uncertain whether FRS is also applicable to Japanese, because it is based on Euro-American data. Mortality from CHD in Japan is considerably lower than Euro-American countries. Studies are needed to assess whether FRS can predict the risk of CHD also in Japanese. At present, the three most common causes of death in Japan are cancer, heart disease, and stroke, leading to 273.5, 143.7 and 97.2 deaths per 100,000 person years, respectively, according to data compiled by The Health, Labour and Welfare Ministry, on the Population Survey Report 2009 Japan (3). The prevention of these diseases is the most important issue in public health in Japan as well as the rest of the world.

These risk factors of CHD such as age, blood pressure, serum cholesterol, diabetes mellitus and obesity are also risk factors of arterial stiffness. Arterial stiffness is associated with a number of deleterious cardiovascular conditions and has been identified as an independent risk factor for CHD.

Although pulse wave velocity (PWV) of the aorta is being used as the standard measure for arterial stiffness in Western countries, it can be measured in some other arterial regions, such as heart-carotid (hc), heart-brachial (hb), and femoral-ankle (fa) segments. The most frequently studied index to date among a variety of PWV measures is the carotid-femoral pulse wave velocity (cfPWV).

In Japan and other Asian countries, the brachial-ankle PWV (baPWV) is now widely utilized, because it can be measured easily and noninvasively. The baPWV is applicable as an indicator of arterial stiffness, which is the case in cfPWV (4).

The purpose of this study was to evaluate determinants of baPWV in the Japanese population.

Methods

This was a sub-analysis of data of the Japan Multi-institutional Collaborative Cohort (J-MICC) Study in Kyoto conducted by Kyoto Prefectural University of Medicine. All of the 528 participants (270 males and 258 females) of this study were general healthy workers of local government offices and companies aged from 36 to 69 and inhabitants of Kyoto Prefecture. Those whose residential addresses were not in Kyoto Prefecture were excluded from this study, because of epidemiological follow-up research. They

participated in this study after receiving an adequate explanation of the study and signing an informed consent form at a routine annual health check in their workplaces. The present study was conducted from July to December 2009. Measurements of blood pressure, baPWV and augmentation index (AI) were conducted after the subjects had rested in the siting position for at least five minutes in the morning, and subjects were not allowed to smoke before the measurement. All measurements were conducted on the annual health check in the work place of the participants. Each of baPWV (S.M.) and AI (E.O.) measurements was done by the same investigators. After the completion all measurements, each participant got a detailed briefing on the results from a physician. This study consisted of subjects with a health check including serum and urine examinations, questionnaire, and blood pressure, baPWV and AI as original items of the Kyoto survey. This study was approved by the ethics committee of Kyoto Prefectural University of Medicine (E-267).

J-MICC Study

The J-MICC Study is a cohort study that was started in 2005 to examine gene–environment interactions in lifestyle-related diseases, especially cancers (5). This study was supported by a research grant for Scientific Research on Special Priority

Areas of Cancer from the Japanese Ministry of Education, Culture, Sports, Science and Technology (6, 7). The J-MICC Study group is composed of 10 cohorts surveyed by 10 independent research teams (8, 9). Kyoto Prefectural University of Medicine is one of these 10 independent research teams. The participants of the J-MICC Study completed questionnaire on lifestyle factors and diseases, donated blood samples, and, in addition, underwent an examinations of blood pressure, PWV and AI at the time of the baseline survey.

baPWV measurement

baPWV was measured using a volume-plethysmographic apparatus (Form/ABI: Omron-Colin, Kyoto, Japan).

Measurements of blood pressure and AI

The blood pressure was determined by a single measurement on the right upper arm using the oscillometric method. Immediately after the measurement, the waveform of the left radial artery was recorded for determining AI using an arterial applanation tonometry probe incorporating an array of 40 micropiezo-resistive transducers (HEM-9000AI: Omron-Colin, Kyoto, Japan).

Definition

Alcohol consumption was classified into two categories depending on the current status, current drinker and no-drinker, because former-drinkers were few.

The smoking status was classified into three categories of current, former, and never smoked. Physical exercise was classified into three categories: one who did not have exercise habit, one who exercised one to three times a month, and one who exercised more than three times a month. The categories of hypertension were classified according to the staging criterion of the Hypertension Guidelines by the Japanese Society of Hypertension Committee (10): optimum BP as SBP<120mmHg and diastolic blood pressure (DBP) <80mmHg, normal BP as 120mmHg=< SBP =<139mmHg and 80mmHg=<DBP=<89mmHg, untreated hypertension as systolic SBP >=140 mmHg and /or diastolic DBP >=90mmHg, and treated hypertension.

Because the observed AI data are influenced by the heart rate, AI P75 was calculated by setting the heart rate at 75 beats/min for the heart rate compensation.

Framingham risk score

The experience of the Framingham study population was used to develop an algorithm

that resulted in a calculated score to predict the 10-year risk of CHD. We calculated the score from the age, sex, smoking status, blood level of total cholesterol (T-Ch), high-density lipoprotein cholesterol (HDL-Ch), and SBP with or without hypertension treatment.

Statistical methods

All data is expressed as the mean±SD. Categorical variables are expressed as a percentage. Pearson's correlation coefficients were used to assess the linear relationship between baPWV and age, SBP, DBP, T-Ch, triglycerides (TG), HDL-Ch, HbA1c, AI P75, body mass index (BMI), and FRS. Differences in each variable between any two groups were evaluated using the t-test. Covariance analysis was also performed to analyze associations of categorized classifications such as alcohol consumption, smoking status, exercise habit, presence of parents' CHD events, and status of hypertension, only in a case in which it was possible to hypothesize parallelism, after assessing the absence of an interaction between each factor and covariates (age and sex). Multiple regression models were used to analyze associations between baPWV and other clinical parameters. P-values less than 0.05 was taken as statistically significant. Analyses were performed using SPSS software package 18 (SPSS, Chicago, IL, USA).

Results

Table 1 shows the characteristics of this study population. The mean age of the subjects was 47.9±8.1 (male: 47.7±8.5, female: 48.1±7.8) years. There were significant differences between males and females, with respect to the height, SBP, DBP, T-ch, TG, HDL-ch, AI P75, baPWV and FRS. Males generally had a poor cardiovascular risk profile compared to females, characterized by a higher BP, higher T-Ch and lower HDL-Ch, higher TG, higher baPWV, higher BMI, and higher FRS. baPWV had a strong correlation with the age (r=0.51), SBP (r=0.65), DBP (r=0.66), and FRS (r=0.53), and a weak correlation with TG (r=0.30), BMI (r=0.28) and AI P75 (r=0.26). (Table 2)

Fig.1 reveals that baPWV was significantly correlated with FRS (total: r=0.53, $p<0.01$, for male: r=0.40, $p<0.01$, for female: r=0.65, $p<0.01$).

Covariance analysis showed the relations among baPWV, AI P75, alcohol consumption, smoking status, exercise habit, presence of parents' CHD events, and status of hypertension (Table 3-a, and 3-b). Regarding baPWV, there were significant differences in exercise habit adjusted by age and sex ($F=3.55$, $p=0.03$) and the status of hypertension adjusted by sex ($F=4.09$, $p=0.04$), after assessing the absence of an interaction. Those who exercised more than three times a month showed a lower

baPWV than those who did one or three times and those who did not have exercise habit in subgroup analysis. As for hypertension, there was an interaction between hypertension and age; thus, covariance analysis was conducted to compare the hypertension status with baPWV using only sex as a covariant. Regarding BP, the BP values of those who received treatment (SBP: 136.4mmHg, DBP: 86.7mmHg) were lower than those who did not (SBP: 141.7mmHg, DBP: 93.4mmHg). However, those with anti-hypertensive treatment showed a higher baPWV than the others. (Table 3-a) On the other hand, regarding AI P75, there were significant differences in alcohol consumption ($F=12.9$, $p<0.01$), smoking status ($F=7.20$, $p<0.01$) and the status of hypertension ($F=5.67$, $p<0.01$). Those who were current drinkers and those who had never smoked showed a significantly lower AI P75. Those with hypertension without treatment showed a higher AI P75 than those with an optimum and normal BP; however, there were no significant differences between those with anti-hypertensive treatment and the others. Those whose parents had experienced CHD events were 139 persons, those whose parents had experienced no events were 305 persons, and those who did not know comprised 88 persons. Regarding both baPWV and AI P75, there were no significant differences between the presence and absence of parents' CHD events. (Table 3-b)

We conducted multivariate linear regression analysis with FRS, BMI, AI P75, alcohol consumption, exercise habit and presence of parents' CHD events. All of the variables were involved, because no correlation coefficient of a variable was over 0.9 after checking a correlation matrix table. The results of multivariable linear regression stepwise analysis are shown in Table 4. The result of ANOVA was significant, and R^2 was 0.33. The Durbin-Watson ratio was 2.06, and there was no separate predictive value over ±3D against the actual observed value. Thus, factors of FRS, BMI, alcohol consumption and AI P75 were related to baPWV.

Discussion

The Korean data which has the same Asian population with Japanese reported that cfPWV was associated with the CVD risk as represented by FRS ($r=0.417$、$p<0.01$) (11). Tanaka *et al.* also reported that baPWV and cfPWV were closely associated with blood pressure, FRS and pre-existing CHD in Japanese.　In their researches, the correlation coefficient of baPWV and FRS (r=0.63) was higher than that of cfPWV and FRS (r=0.48). (12)　Many previous studies reported a correlation between baPWV and FRS, and our study also confirmed this. The stiffness of vessels showed by baPWV had a good correlation with lifestyle parameters being risk factors showed by FRS.

However, only FRS did not determine the stiffness of vessels. There were a lot of relative factors on baPWV showed in Table 2. It was a fact that FRS shows a strong correlation with baPWV, however, age, gender and BP tended to be stronger factors correlated with baPWV. Although diabetes was reported to be an evident factor of CHD and stroke in NIPPON DATA (13), our study showed that there was no statistically significant correlation between HbA1c and baPWV (r=-0.03, p=ns). Our data was an accurate assessment regarding the correlation between the abnormal glucose tolerance and the stiffness of vessels, while NIPPON DATA addressed the mortality and occasional blood glucose level. On the other hand, another study reported that diabetes mellitus had a significant correlation with baPWV (14). Thus, further research will be needed to clarify the relation between diabetes and baPWV.

Covariance analysis showed conflicting results regarding alcohol consumption and smoking between baPWV and AI P75. Although baPWV reflects the stiffness of vessels, AI does the ratio between reflected and ejected waves (15). The bigger a reflected wave, and the shorter the returning time of a reflected wave, the bigger the value of AI. AI denotes systolic overload of the left ventricle (impedance).

In the presence study, smoking status and alcohol consumption affected not baPWV but AI 75. Current drinker and never-smoker revealed significantly milder overload of the

left ventricle than their counterparts. However, multivariate linear regression analysis showed a significant effect of alcohol consumption on baPWV, which is interpreted by a fact that beverages provide protection against an oxidative stress in blood vessels and decrease arterial stiffness (16).

Although our study did not analyze the intensity and kind of exercise, our results showed that exercise with high frequency made blood vessels smoother, and reduced the overload for heart. It has been shown that regular aerobic exercise is associated with reduction in CHD morbidity and mortality (17). Several studies have also shown that aerobic exercise improves endothelium-dependent vasodilation (18). Another study has revealed that moderate aerobic exercise reduces endothelin-1-mediated vasoconstrictor tone (19). These mechanisms allow vessels to be smoother by aerobic exercise. Indeed, some studies reported that exercise caused cfPWV reduction in patients with hypertension (20). Our study supported these findings in a healthy Japanese population.

On the other hand, history of parents' CHD is also reported to be a risk factor of CHD in the USA. Some epidemiological studies including prospective studies reported that the family history was independent of other risk factors (21, 22). However, our results were disagreement with above mentioned findings. This may be explained, at least in part, by

the fact that questionnaire was badly-phrased one, or general participants could not remember the history of their parents' diseases.

More noteworthy was influence of hypertension. The blood vessels of those who had anti-hypertensive treatment indeed were stiffer as shown in table Ⅲ-a, however, the overload for heart were lower than those who did not have treatment as shown in table Ⅲ-b showed.

The difference between arterial stiffness and AI75 may be explained as follows.

It is assumed that arterial stiffness is determined by pathological characteristics of large conductance arteries which seem to be stable for a long period regardless of anti-hypertension treatment. In contrast, AI75 is influenced by peripheral arterial tone which is sensitive to anti-hypertensive treatment.

These findings suggest that treatment for hypertension is probably useful to prevent the occurrence of CHD. Some previous studies have demonstrated that hypertension is an independent risk factor of CHD even when adjusted by other factors. A dose-response relationship, whereby an increased BP is associated with an increased risk of the development of CHD, could be realized. The Hisayamacho study, which is one of the most famous epidemiological studies in Japan, reported that the extent of arterial stiffness was significantly correlated with SBP of both the start of the study and just prior to death (23).

However, there may be some complicated mechanisms regarding how increased SBP leads to CHD occurrence in Japanese. Hirai Y, *et al.* reported that SBP is used to predict cardiovascular mortality in a farming but not in a fishing community in a 40-year follow up of Japanese cohorts in the Seven Countries Study (24).

Additionally, baPWV had relation with not only FRS but also BMI, alcohol consumption, and AI75 as shown in table Ⅳ. The Framingham study reported that obesity was an independent risk factor compared with age, smoking status, total cholesterol levels, SBP, diabetes mellitus and cardiomegaly from their 26-year investigation (25). Although there are numerous studies indicating the correlation between obesity and CHD, FRS does not include the factor of obesity. Our study indicated that BMI was an independent risk factor for arterial stiffness.

Conclusions

1) The FRS and baPWV show a good correlation. FRS seems to be applicable as an index of arterial stiffness also in Japanese.

2) Blood pressure in patients with anti-hypertensive treatment is well controlled; however, vessels are still stiff, whereas the AI is considerably low. These findings suggest that anti-hypertensive treatment is probably useful to prevent CHD.

Acknowledgment

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Fig. Ⅰ. Correlation plots between brachial-ankle pulse wave velocity and Framingham risk score.

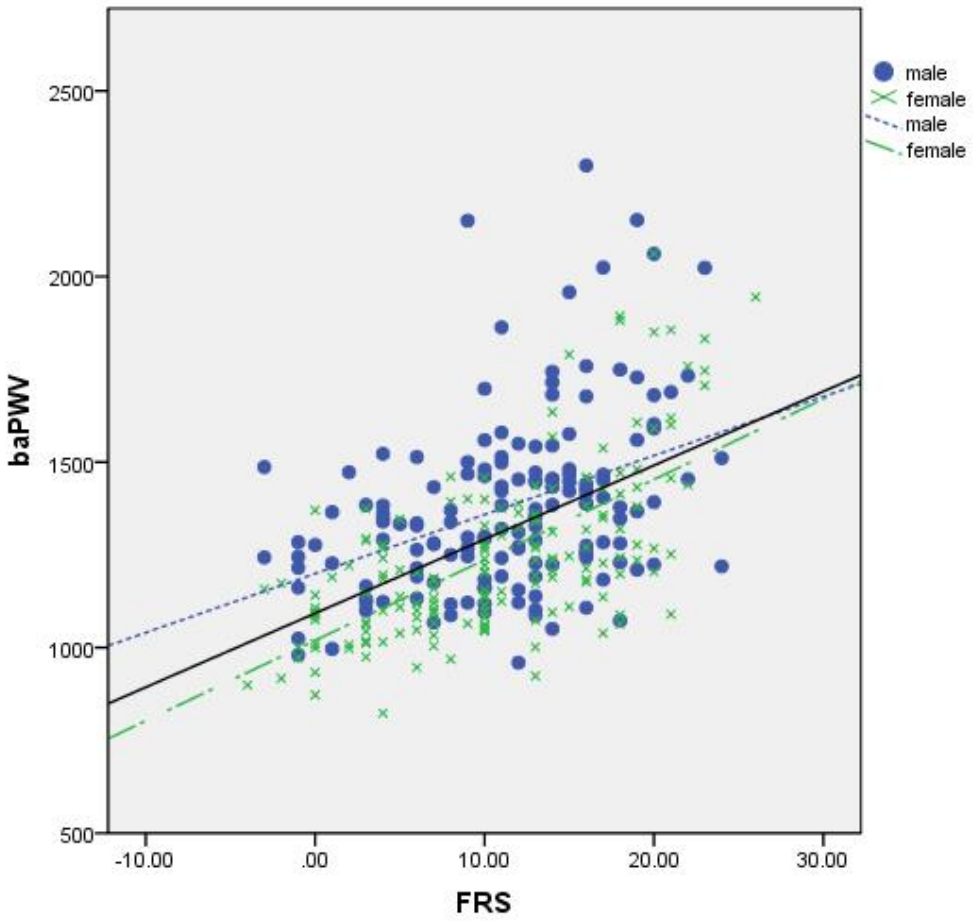

Figure legend

Closed circle means male, cross means female. The dotted line means male (r=0.40), dashed-dotted line means female (r=0.65), and continuous line means total of male and female (r=0.53).

baPWV: brachial-ankle pulse wave velocity, FRS: Framingham risk score.

Table Ⅰ. Characteristics of the participants

	Total	Male	Female	t	P value
Total number of subjects (%)	528	270 (51.1)	258(48.9)		
Age (years)	47.9±8.1	47.7±8.5	48.1±7.8	0.54	0.59
Height (cm)	163.7±9.0	170.4±5.7	156.6±5.7	27.64	<0.01
SBP (mmHg)	120±16	127±15	115±16	7.73	<0.01
DBP (mmHg)	74±11	78±11	70±11	7.59	<0.01
T-ch (mg/dL)	204±36	198±37	210±35	2.88	<0.01
TG (mg/dL)	106±64	129±67	88±55	7.09	<0.01
HDL-ch (mg/dL)	64±16	57±14	69±16	8.95	<0.01
HbA1c (%)	5.0±0.5	5.0±0.6	5.1±0.5	1.31	0.19
HR (beats/min)	66±11	67±11	66±11	0.14	0.89
AI P75	72.4±14.4	66.7±13.6	78.3±12.6	10.10	<0.01
baPWV (cm/sec)	1,305±230	1,367±220	1,243±14	6.40	<0.01
BMI (kg/m^2)	22.5±2.9	23.4±2.8	21.6±2.8	7.34	<0.01
FRS	10.9±6.5	11.4±6.0	10.5±6.8	1.21	<0.01

SBP: systolic blood pressure
DBP: diastolic blood pressure
T-ch: total cholesterol
TG: triglyceride
HDL-ch: high-density lipoprotein cholesterol
HR: heart rate
AI P75: augmentation index pulse 75
baPWV: brachial-ankle pulse wave velocity
BMI: body mass index
FRS: Framingham risk score

Table Ⅱ. Correlations between factors related to baPWV

	Age	SBP	DBP	TG	T-ch	HDL-ch	HbA1c	AI P75	BMI	FRS
baPWV	0.51**	0.65**	0.66**	0.30*	0.08	-0.16*	-0.03	0.26*	0.28*	0.53**
Age		0.27*	0.26*	0.14*	0.18*	-0.07	0.04	0.41*	0.11*	0.81*
SBP			0.80*	0.30*	0.03	-0.19*	-0.16*	0.15*	0.40*	0.37*
DBP				0.29*	0.08	-0.17*	-0.08	0.19*	0.37*	0.35*
TG					0.15*	-0.48*	-0.17*	-0.05	0.40*	0.31*
T-ch						0.24*	0.08	0.12*	0.09	0.55*
HDL-ch							0.08	0.14*	-0.40*	-0.12*
HbA1c								0.18*	-0.05	0.05
AI P75									-0.10*	0.36*
BMI										0.28*

**: $p<0.01$, *: $p<0.05$

Table Ⅲ-a. Covariance analysis of baPWV adjusted by age and sex

		N (%)	Estimated baPWV	Adjusted by	F value	P-value
Alcohol consumption						
	Current drinker	310 (58.4)	1,308±11	Age and sex	0.05	0.82
	No-drinker / past-drinker	221 (41.6)	1,304±13			
Smoking						
	Current smoker	108 (20.3)	1,316±20	Age and sex	0.22	0.81
	Former smoker	90 (16.9)	1,314±21			
	Never	333 (62.7)	1,302±11			
Physical exercise						
	Nothing	111 (20.9)	1,349±18	Age and sex	3.55	0.03
	1-3 times/month	120 (22.6)	1,303±17			
	More	301 (56.6)	1,292±11			
Presence of parents' CVD event						
	Yes	139 (26.1)	1,320±16	Age and sex	0.55	0.58
	No	305 (57.3)	1,303±11			
	Unknown	88 (16.5)	1,296±21			
Hypertension						
	Optimum BP	204 (38.3)	1,153±13	Sex	4.09	0.04
	Normal BP	156 (29.3)	1,318±14			
	Hypertension without treatment	112 (21.1)	1,463±17			
	Hypertension with treatment	50 (9.4)	1,537±25			

Table Ⅲ-b. Covariance analysis of AI adjusted by age and sex

		N (%)	Estimated AI75	Adjusted by	F value	P-value
Alcoholl consumption						
	Current drinker	306	70.7±15.1	Age	12.9	< 0.01
	No-drinker / past-drinker	219	74.6±13.2			
Smoking						
	Current smoker	108 (20.3)	76.6±1.2	Age and sex	7.20	< 0.01
	Former smoker	90 (16.9)	72.4±1.3			
	Never	333 (62.7)	71.0±0.7			
Physical exercise						
	Nothing	110	74.3±1.2	Age and sex	1.87	0.16
	1-3 times/month	118	72.7±1.1			
	More	298	71.6±0.7			
Presence of parents' CVD event						
	Yes	139	72.0±1.0	Age and sex	0.37	0.69
	No	305	72.4±0.7			
	Unknown	84	73.4±1.3			
Hypertension						
	Optimum BP	202	70.1±0.9	Age and sex	5.67	<0.01
	Normal BP	156	72.1±1.0			
	Hypertension without treatment	111	76.2±1.1			
	Hypertension with treatment	50	72.8±1.7			

Table Ⅳ. Multivariable liner regression analysis between baPWV and risk factors

	Unstandardized coefficient	Standardized coefficient	p-value	95% CI	
Invariable	694.86	119.10	<0.01	460.51	929.22
FRS	15.88	2.01	<0.01	11.93	19.83
BMI	14.48	4.11	<0.01	6.41	22.56
Alcohol	-33.30	11.42	<0.01	-55.78	-10.83
AI P75	2.44	0.87	<0.01	0.74	4.15

CI: confidence interval

Abbreviations are same as in Table Ⅰ.